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February 1, 1979

Hearing Clerk (HFA-305)
Food and Drug Administration
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20852

Re: Docket No. 78N-0065, Skin Bleaching Drug Products for Over the Counter Human Use; Establishment of a Monograph; Notice of Proposed Rulemaking

Gentlemen:

The above referenced proposed rule was published in the November 3, 1978 Federal Register and would, if adopted, establish conditions under which over-the-counter "skin bleaching" drug products are generally recognized as safe and effective and not misbranded. Members of the public were invited to submit comments by February 1, 1979.

Nicholas Products, Ltd. (Nicholas) is a manufacturer and distributor of products which would be affected by the proposed rule. Nicholas is one of four manufacturers which made submissions to the Advisory Review Panel on OTC Miscellaneous External Drug Products in connection with the deliberations which resulted in the proposed rule. Nicholas is herein submitting its comments on the agency proposal.

78N-0065

C00002

Nicholas respectfully requests the Agency to consider the following:

I. The term "skin bleaching" does not accurately describe the function of the products covered by the proposal

The Panel has found that the products it reviewed in connection with this proposal were designed to "lighten limited areas of hyperpigmented skin." The Panel also has recognized that the depigmenting effect is reversible; after cessation of treatment, repigmentation occurs. (p. 51550, 51551, citing literature references by Arndt and Fitzpatrick, Denton et al., and Spencer).

Nicholas agrees with both of these observations, but submits that the term "bleaching" is inconsistent with the products' described functions and could result in considerable consumer misunderstanding. It has been Nicholas' experience that consumers associate the term "bleaching" with "whitening;" and that many consumers perceive a "bleaching" effect to be both harsh and permanent. This is probably because consumers usually encounter the term in connection with laundry bleaches, the purpose of which is quite different from the skin depigmenting products.

Hydroquinone preparations at appropriate concentrations are neither harsh (e.g., "[t]heir use has not been shown to produce significant systemic or local toxicity," 43 F.R. 51551) nor do they result in the permanent lightening or

or "whitening" of the skin. In addition, the use of a term which connotes "whitening" would be offensive to those black consumers */ who use the products to lighten unusually dark patches of skin in order to produce a more even skin tone. An informal survey conducted by Nicholas indicates that of four possible statements describing the function of these products, "skin bleaching" was rated "most offensive" by nearly half of the black women surveyed, while "skin color toning" was rated "least offensive." **/

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*/ Well-over 50% of the total sales of the products under consideration are to black consumers.

**/ 85 black women were shown the following four terms: "skin bleaching cream," "skin color toning cream," "skin cream which lightens dark pigment to produce an even toned appearance," and "skin lightener cream." Each subject was asked to select the phrase found "most offensive" and the phrase found "least offensive." The results were:

Phrase	Number who selected as most offensive	Number who selected as least offensive
Skin bleaching	40(45%)	11(13%)
skin color toning	7(8%)	47(55%)
skin cream which lightens	24(28%)	18(21%)
Skin lightener	14(16%)	8(9%)
No preference	--	1(1%)

Nicholas proposes that §358.50(a)(c)(1) and (c)(2) be modified to delete all references to "bleaching" and to substitute the term "skin color toning." A second acceptable alternative, which would be less preferable to consumers than "skin color toning" but nevertheless more accurate than "bleaching" would be the term "skin depigmenting" agent. Although Nicholas is most concerned with the terminology to be required in labeling, to be consistent, all other references in the monograph to "bleaching" should also be appropriately modified.

II. The permitted indications should be expanded.

Many consumers, including blacks, use depigmenting agents on hyperpigmented areas of skin to produce an even skin coloration or "tone." Because these consumers understand the term "skin tone" to include this use, an expanded indication incorporating the term would add clarity and permit a better understanding of the intended use of the product. It is requested that §358.50(b) be amended by the addition of a new subparagraph (3) to read as follows: "(3) 'Lightens dark pigment in the skin to produce a more even skin tone.'"

III. The Panel's Classification of Certain Claims as Category II is inconsistent with the cosmetic functions of the products, is unnecessarily restrictive and is legally unsupportable

The skin depigmenting agents under consideration are drugs which are used for essentially "cosmetic" purposes, i.e., to alter the user's appearance in a way the user finds appealing. They are, in this sense, similar to the mass of cosmetic products which have traditionally been marketed to achieve visual effects which mask or enhance certain natural features. The proposal recognizes the cosmetic purposes of the depigmenting agents in noting, e.g., that melanism and senile lentigines may be "cosmetically unappealing" to the patient; (p 51550) that the earlier treatment is begun, the more likely "a satisfactory cosmetic result" (p 51550); and that abnormal variation in skin color "constitutes a cosmetic liability." (p 51551)

Nicholas urges that these products should be allowed to be promoted in a manner consistent with their cosmetic purposes, i.e., by encouraging users to use them to promote attractiveness. An assessment as to whether the depigmenting effects of these products promotes attractiveness */, and

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*/ It should be noted that in addition to the depigmenting drug ingredient, many of these products contain traditional cosmetic (inactive) ingredients, such as moisturizers, which are added solely for the purpose of improving one's appearance.

thereby improves one's appearance or looks, is best judged by the consumer's own perceptions rather than by scientific data or reference to "pharmacologic properties."

With reference to the examples of Category II claims listed in paragraph (a) under that heading, it is urged that a distinction should be drawn between (1) claims that use of the product "results in healthier, younger, or rejuvenated skin," which are traditional "drug" claims and should not be made without substantiating data, and (2) claims that use of the product results in healthier or younger looking skin, which are "cosmetic" claims and should not be prohibited. The Category II classification, as now worded, would appear to prohibit both types. Examples of the latter "cosmetic" type claim which would be unnecessarily prohibited under the current proposal are "gives a more even-tone wholesome looking coloring," "helps fade the brown spots that tend to make your skin look older," and "helps skin look fairer, clearer, younger."

Further, it makes no sense to place a claim such as "helps skin look younger" or "helps fade...blemishes which can make your skin look older" in Category II, while permitting the Category I indication "for the gradual fading of 'age spots'." We propose that the Category II labeling section be modified so as to make it clear that it does not prohibit

"cosmetic" claims and to reflect the distinction between those claims and "drug" claims. Moreover, it is respectfully submitted that the OTC Panel lacks jurisdiction to make recommendations with respect to cosmetic claims and that the legal standards applicable to cosmetic claims are, for the reasons enumerated above, different than those applicable to drug and new drug claims.

Certain other claims currently placed in Category II also require clarification or modification. For instance, the Category II prohibition on claims for use where skin has become discolored, spotted or darkened from bad weather or natural aging could be construed to prohibit the Category I claims for "age spots," "liver spots," freckles and melasma. It is unlikely that this was the Panel's intent, but without clarification it is difficult to tell which aspects of the prohibited claim trigger the prohibition.

Finally, for the many blacks who use such products on hyperpigmented areas, the term "blotchy skin" is their indication for use of the product. Accordingly, we propose that the claims "for skin that appears blotchy due to uneven pigmentation," "skin color blotches" and "fades dark blotches" be specifically permitted.

IV. Certain wording in the proposed warnings should be modified to more accurately correspond to the properties of the products.

The proposal stresses (§358.50(c)(1)) use of the warning "Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from recurring." This warning is unnecessary for combination products which already contain an effective sunscreen agent, and the monograph should provide that it need not appear on these products. Otherwise, the warning encourages users of combination products to "double up" on drug use.

Even for hydroquinone products without a sunscreen, "indefinite avoidance" of sunlight is unrealistic if not impossible. We suggest a more reasonable warning, intended to accomplish the same caution: "To help prevent reversal of the effects of this product, exposure to sunlight should be limited by use...." In addition, for the reasons set forth above, the reference in this warning to "bleached skin" should be deleted.

In any event, it is submitted that the available data do not indicate danger of a type and severity which would require that the sun exposure warning should be conspicuously boxed and in red letters. In this regard it is important to

note that the "warning" under consideration is addressed not to an issue of safety but to one of efficacy.

Warning (iv) would encourage discontinuance of use if changes were not achieved within a two-month period. Nicholas' experience as a manufacturer of hydroquinone products has been that although the majority of users achieve intended results within two months, some users require longer. We recommend that "three months" or "prolonged use" be substituted for "two months."

Warning (v) should be changed from "in children" to "on children."

Warning (vi), which states that users with very dark skin may not noticeably respond, is unnecessary and contrary to the body of available data. Generally, the data indicate that hyperpigmented patches ("blotches"), are most susceptible to depigmenting treatment. Attached is the report of an animal study showing noticeable changes on very dark skin. (Also see, Hu, F., The Influence of Certain Hormones and Chemicals on Mammalian Pigment Cells" Journal of Investigative Dermatology 46:117-124 1966). We urge that this warning be deleted.

V. <u>The directions should be clarified</u>

We believe the directions set forth in §358.50(d) would be better understood and followed by lay consumers if revised

to read as follows: "Directions -- For adults, apply twice daily to the affected areas or use as directed by a physician. For children under 12, use only on the advice and direction of a physician."

VI. Combination policy should be clarified

Proposed §358.20 states that hydroquinone combined with a safe and effective sunscreen agent will be permitted "provided that the product is labeled only as identified in §358.50." Use of the word "only" in this sentence invites the interpretation that any reference, other than that in the ingredient statement, to the presence and function of the sunscreen agent would be prohibited. The policy should be clarified so that it is made clear that the labeling for combination products may state that the product contains an effective sunscreen agent which is designed to minimize the sun's reversing effect. Under proposed §358.20 a mandatory condition for combining hydroquinone with a sunscreen agent is that the sunscreen agent be generally recognized as safe and effective. This fact, taken in conjunction with the recognized need for the concurrent use of a sunscreen agent, makes it incongruous to prohibit a truthful and not misleading statement as to the intended beneficial effect of the sunscreen agent.

VII. The conclusion in the preamble (43 Fed. Reg. 51549) that "prolonged use of high concentrations (5 percent or more) of hydroquinone with exposure to the sun may produce disfiguring effects" is potentially misleading.

The Panel's adverse conclusions regarding concentrations of 5 percent or more is based on reports of disfiguring effects referenced in only one paper (Findlay, et al., p. 51553, Ref. (5)), while a similar study (Arndt and Fitzpatrick, p. 51553, Ref. (6)) reported no such effects, even though a 5 percent concentration was used. It is submitted that the present data on safety and efficacy of higher concentrations is simply inconclusive, and accordingly the above-referenced conclusionary statement is misleading and should be deleted.

Respectfully submitted,

KLEINFELD, KAPLAN AND BECKER

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AN EVALUATION OF A COSMETIC CREAM CONTAINING 2% W/W OF HYDROQUINONE AS AN AGENT FOR REDUCING THE DARKNESS OF BLACK SKIN

1/26/79

SUMMARY

A cosmetic cream (footnote AMBI Skin Toning Cream 2% HQ Nicholas International Ltd.) was evaluated for its toning effect on skin using the black pig as an animal model.

Using daily visual observations as well as objective histological evaulation techniques, the formulation under examination was shown to produce a lightening of black skin compared with a control area of skin on the same animal.

INTRODUCTION

Pigs have been used extensively in biomedical research (References 1 and 2) and have been shown to have a close correlation with human tissues and pharmacodynamics. This is particularly true for skin structure and function, and indeed pig skin has been used as skin grafts to replace areas of extensive skin damage in humans. For these reasons, the black pig has been used as the animal model in a series of experiments which have been carried out over the past two years.

METHODS

1. Animals. Very black pigs weighing 80-200 lbs. were housed in individual stalls in a specific pathogen-free environment with a controlled atmosphere. Two pigs were used in the examination of the effect of the application of the formulation. Duplicate sets of patches approximating the area of the human face were marked along each side of the pigs providing a complete set of control and test sites on each side. One side of each animal was irradiated twice daily in an attempt to simulate the effect of sunlight in the normal human experience.

2. Administration of Test Product. Following preparation of the skin surface by shaving, the sites were designated as control and test areas. Control sites had no application of cosmetic cream, but were otherwise treated in a similar manner to the test areas. Test sites were treated by applying a measured quantity of the cream as a uniform thin film by means of an applicator in a standard and reproducible manner twice daily.

3. Sunlight Exposure. The radiation was derived from a solar simulator and administered as a fixed dose twice daily calculated to approximate a casual human exposure.

4. Visual Appearance. This was done subjectively by two independent observers who made daily comparisons of test and control areas under standard lighting. These were descriptively recorded and a color photograph incorporating a reference color chart and date label was taken at regular intervals to record any significant change.

5. Histological Examination. Preliminary studies, using a new process for histological tissue embedding to reduce artefactual shrinkage, had shown that skin biopsies examined by light microscopy gave a close correlation with the depth of color observed in the living skin. Biopsies were taken at regular intervals in both control and test sites and at times of particular interest. The examination of these samples was done "blind" by a senior specialist pathologist and the written evaulations were later correlated with the record of daily skin observations.

6. Ultrastructural (Electron Microscope) Examination. A portion of each biopsy was processed for examination by electron microscopy. Preliminary studies had shown that this, too, gave a close correlation with observed color changes. It was felt that the capacity for higher magnification (up to X 100,000) may allow closer analysis of the way color changes occur, as well as yielding more statistical morphometric data of color intensity and distribution of melanin (dark skin pigment). These studies are very time consuming and expensive and, although incomplete at this stage, expect to be finished within months.

Results

Summary of Experimental Observations. On visual appearance and the corresponding histological evaluation, the cosmetic cream containing 2% hydroquinone produced a marked reduction in the intensity of the skin blackness, when compared with the control areas. The effect was definite at nine days and was observed throughout the total observation period of six weeks. (Figures 1 and 4).

Discussion

Both the daily recorded observations and the histological preparations examined "blind" showed a close correlation and consistently indicated that the 2% hydroquinone in cosmetic cream produced an area of skin color lighter than the control areas. The color photographic record of skin appearance incorporating reference color comparitive charts was found to be a less reliable objective record of changes than the descriptions, and was of little value as an illustration of the changes observed.

References

1. Bustad, L.K. and McClellan, R.O. 1965. "Use of Pigs in Biomedical Research." Nature (London). Issue 208, page 531.

2. McIver, M.A. and Hobbs, J.B. 1975. "The Failure of High Doses of Aspirin to Produce Renal Lesions in Pigs." Medical Journal of Australia 1975. Issue 1, pages 197-199.

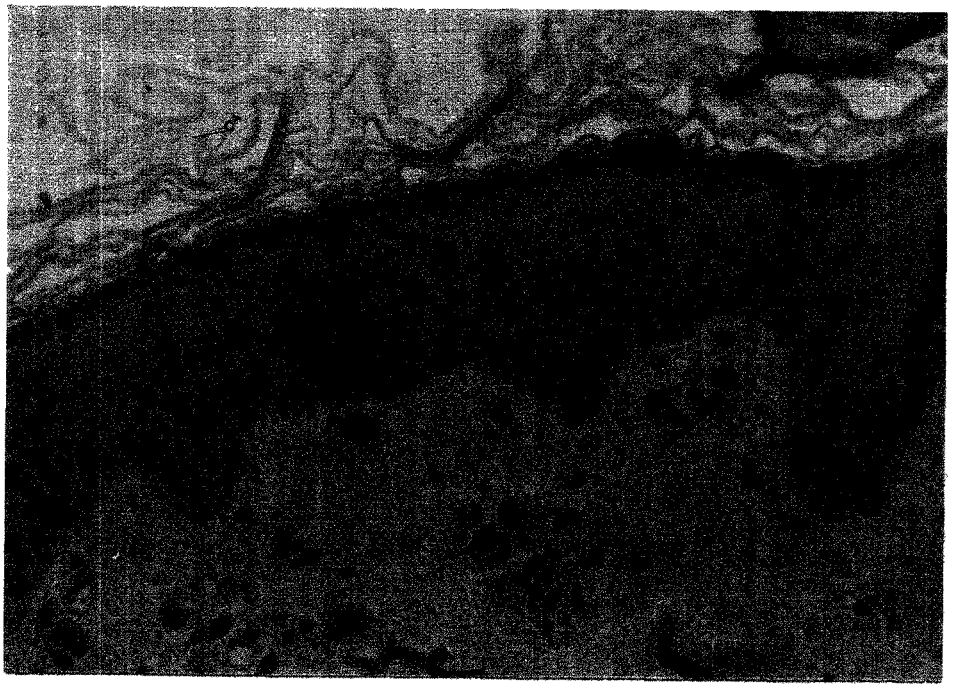

Figure 1.

From test site Section of skin on 9th. Day of Trial.
Arrows show isolated melanin granules. (Mag. x 1000).

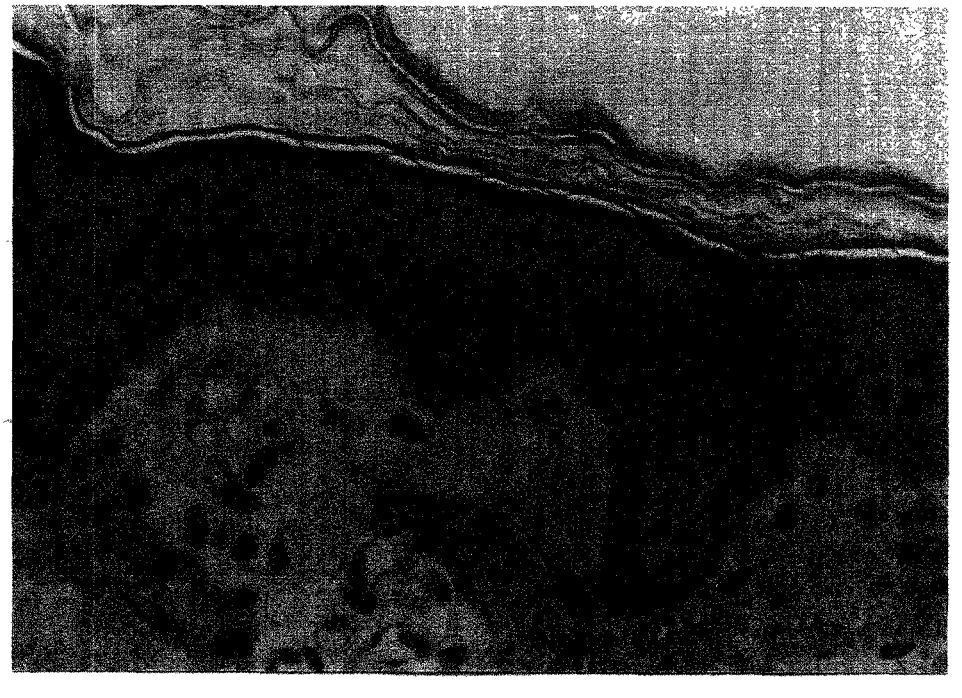

Figure 2.

Section of skin from untreated control on 9th. Day of Trial.
Arrows show melanin clusters.
(Mag. x 1000)

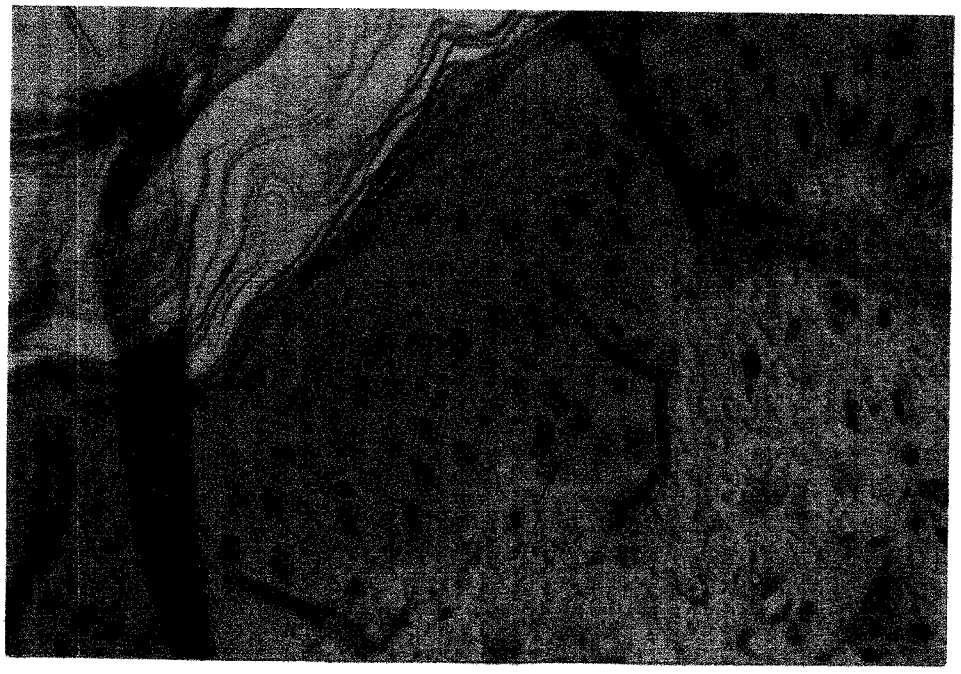

Figure 3.

Section of skin from test site after 6 weeks of trial. Arrows show isolated and diminished melanin granules. (Mag. x 1000).

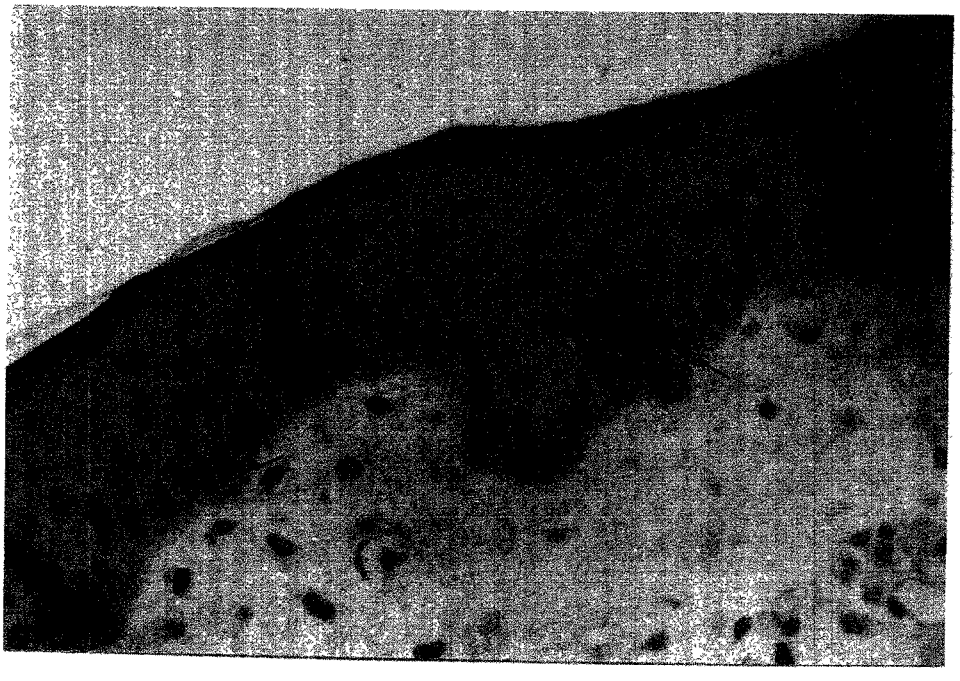

Figure 4.

Section of skin from untreated control after 6 weeks of trial. Arrows show melanin clusters. (Mag. x 1000)